REMARKS

The amendments above conform the specification and claims to the requests contained in the Office Action mailed September 9, 2004.

1 Amendments to the Specification

Applicants have also taken this opportunity to correct various typographical errors in the specification. For example, at page 25, line 1, the term "Trp-Pro-Lys-His-Xaa-NH_2" has been replaced with the term --Trp-Trp-Pro-Lys-His-Xaa-NH_2-- in order to correct a typographical error. Support for this amendment can be found at column 1, line 66-67 of U.S. Patent No. 5,641,861, which was incorporated by reference in the present application.

2 Unavailability of Parent Application

The examiner noted that the parent application, 09/134,803 is unavailable, and that the examiner will review the references listed in the November 19, 2003 IDS when the parent application becomes available. If the parent application remains unavailable, the applicants would be happy to resubmit the IDS with copies of the documents for consideration by the Examiner. The Examiner is requested to contact the undersigned by telephone or email (jerryclarke@mvalaw.com) should this become necessary.

3 Sequence Listing

A copy of the Sequence Listing in computer-readable form (on compact disk) and in paper copy (32 pages, attached as Appendix A) are enclosed herewith. I hereby state that the contents of the paper and computer readable copies of the Sequence Listing are the same. I also hereby state as required under 37 C.F.R. § 1.821(h) that the computer readable copy and the paper copy of the sequence listing submitted concurrently herewith contains no new matter, nor does it go beyond the disclosure of the application as filed. Applicants respectfully request that the present application be amended to incorporate the Sequence Listing. A separate transmittal letter is enclosed herewith for the compact disk in accordance with 37 C.F.R. § 1.52(e).

4 Enablement of Pending Claims

In the Office Action, the pending claims were rejected as lacking in enablement. The enablement requirement is satisfied where there is "sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. [T]he disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed

utility."[1] "The fact that some experimentation is necessary does not preclude enablement; all that is required is that the amount of experimentation must not be unduly extensive." [2]

In order to expedite the allowance of the application, the applicants have narrowed the claims, while reserving the right to pursue broader claims in a separate application. As narrowed, the claims recite a specific set of peptides "enkephalin peptides," and the description of the oligomer has been modified to recite "a fatty acid moiety having from 4 to 26 carbons coupled to a polyethylene glycol moiety having from 1 to 7 polyethylene glycol units." The pending claims clearly satisfy the enablement requirement. Multiple examples of compounds within the scope of the pending claims are exemplified in the Examples beginning at page 38 of the application as filed. Moreover, the specification describes how to make, use and screen other compounds within the scope of the invention.

The applicants respectfully point out that the Examiner appears to have misread the implications of the data presented at page 47 of the application.[3] The data presented at page 47 demonstrate a remarkable improvement in bioavailability of the conjugated enkephalins relative to unconjugated enkephalin. Unconjugated enkephalin administered peripherally provides no analgesic effect. In contrast, all of the applicants' conjugated enkephalins appear to have traversed the blood brain barrier to produce an analgesic effect of at least 77% compared to morphine at five minutes and 73% compared to morphine at 30 minutes. The examiner questioned the applicability of the conclusions on page 48 to this data.[4] However, the conclusions on page 48 are directed to a different set of data. The conclusions relative to the table on page 47 are found immediately preceding the table.

5 Novelty of the Pending Claims

The Examiner cited Ekwuribe (5,681,811) as rendering the applicants claims lacking in novelty. As amended, the applicants' claim 53 recites coupling an enkephalin polypeptide to an oligomer, where the oligomer comprises "a fatty acid moiety having from 4 to 26 carbons coupled to a polyethylene glycol moiety having from 1 to 7 polyethylene." Further, claim 53 is amended to recite that the modified enkephalin peptide must "retain analgesic activity." Although Ekwuribe teaches amphiphilic conjugation, Ekwuribe does not describe the specific advantages of coupling an enkephalin polypeptide to the specific set of oligomers. Consequently, the applicants' claims, as amended, overcome the novelty rejection based on Ekwuribe '811.

---

[1] *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir., 1991)
[2] *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).
[3] At page 3 of the Office Action, the Examiner states: "On page 47 of the specification, enkephalin conjugates are shown as compared to the active moiety unconjugated and the data would indicate none of the conjugates increase the activity of the moiety at the same dose or for the same period of time."
[4] At page 3 of the Office Action, the Examiner states: "There is a statement of results on page 48 but it is inconsistent with the data presented."

6 Nonobviousness of the Pending Claims

a. Ekwuribe Patent – Claims to 53-57 and 59-60

Ekwuribe (6,191,105) was cited as rendering the originally submitted claims obvious.[5] As described in section 5 above, the applicants' claims have been modified to recite conjugation of an *enkephalin polypeptide* to a specific set of oligomer moieties in order to achieve a specific effect. Ekwuribe does not teach nor suggest the specific set of compounds recited by the presently pending set of claims. Consequently, the applicants' claims, as amended, overcome the obviousness rejection based on Ekwuribe '105.

b. Ekwuribe and Shashoua – Claim 58

Ekwuribe (6,191,105) and Shashoua (4,933,324) were cited as a combination rendering the originally submitted claim 58 obvious.[6] As noted by the Examiner, Shashoua teaches fatty acid derivatives. In contrast, the applicants' claims recite amphiphilic derivatives. Moreover, claim 53, from which claim 58 depends has been amended to require an "amphiphilic oligomer comprising a fatty acid moiety having from 4 to 26 carbons coupled to a polyethylene glycol moiety having from 1 to 7 polyethylene glycol units," and to require that the use of such oligomer "provid[e] a modified enkephalin peptide having altered binding affinity to its receptor yet retaining analgesic activity...." These specific limitations are not taught nor suggested by the cited references; consequently, claim 58 is nonobvious and is now in condition for allowance.

c. Ekwuribe and Dooley – Claim 64

Ekwuribe (6,191,105) and Shashoua (4,933,324) were cited as a combination rendering the originally submitted claim 64 obvious. As noted above with respect to Ekwuribe and Shashoua, claim 53, from which claim 64 depends has been amended to require an "amphiphilic oligomer comprising a fatty acid moiety having from 4 to 26 carbons coupled to a polyethylene glycol moiety having from 1 to 7 polyethylene glycol units," and to require that the use of such oligomer "provid[e] a modified enkephalin peptide having altered binding affinity to its receptor yet retaining analgesic activity...." These limitations are not taught nor suggested by the cited references; consequently, claim 64 is nonobvious and is now in condition for allowance.

---

[5] See page 5 of the Office Action, last paragraph.
[6] See page 6 of the Office Action, third paragraph.

7 New Claims

The applicants present new claims 65-82 further distinguishing the claimed invention from the cited art. These claims recite a number of specific arrangements of enkephalin peptide conjugates, and nothing in the cited art teaches nor suggests that the use of the specific approaches would yield a "modified enkephalin peptide having altered binding affinity to its receptor yet retaining analgesic activity..." as required by the limitations of claim 53.

Thus for example, the cited art does not teach nor suggest the use of an oligomer where the "fatty acid moiety has from 14 to 22 carbon atoms" (claim 65) or where the "polyethylene glycol moiety has from 1 to 5 polyethylene glycol units" (claim 66) with an enkephalin peptide to yield a "modified enkephalin peptide having altered binding affinity to its receptor yet retaining analgesic activity..." A similar analysis applies to claims 67-76.

Claim 77 recites an "enkephalin peptide conjugate [that] produces its intended pharmacological effect without cleavage of the oligomer." This claim is supported, inter alia, at paragraph 0041 of the application as published. In contrast, the focus of Shashoua is prodrugs. The title is "Fatty acid-neuroactive drug conjugate as a ***prodrug***."[7] "The invention involves the formulation of a ***prodrug***..."[8] Nothing in Shashoua teaches or suggests the making of an enkephalin peptide conjugate that is not a prodrug.

Claim 78 recites an "enkephalin peptide conjugate [that] produces an analgesic effect when administered peripherally." Nothing in the cited art teaches nor suggests that an enkephalin peptide modified using an oligomer "having from 4 to 26 carbons coupled to a polyethylene glycol moiety having from 1 to 7 polyethylene glycol units" as recited in claim 53 would yield a drug that "produces an analgesic effect when administered peripherally."

Claim 79, 80, and 81 are further distanced from the prior art by requiring combinations of the novel elements of claim 76, 77 and 78.

Finally, claim 81 recites "an amphiphilic oligomer comprising a lipophilic moiety coupled to a polyethylene glycol moiety having from 1 to 7 polyethylene glycol units, wherein the polyethylene glycol moiety is coupled at the N-terminus of the enkephalin peptide conjugate, and wherein the lipophilic moiety is an alkyl moiety or a fatty acid moiety." None of the foregoing limitations are taught nor

---

[7] Emphasis added.
[8] First sentence of Abstract (emphasis added).

suggested by the cited references for producing a "modified enkephalin peptide having altered binding affinity to its receptor yet retaining analgesic activity..." as required by the limitations of claim 53.

8 Double Patenting

Claims 53-60 and 64 are rejected under the judicially created doctrine of obviousness-type double patenting based on US Patent 6,309,633. The applicants submit herewith a terminal disclaimer, disclaiming the terminal portion of the term of any patent granted in the present application extending beyond the expiration date of US Patent 6,309,633, thereby obviating the double patenting rejection.

9 Indefiniteness

The Examiner rejected claims 53-60 and 64 under 35 USC § 112, second paragraph, as being indefinite.

In particular, the Examiner noted that in claim 53, line 1, "the binding affinity" lacks antecedent basis. As amended, claim 53 now recites "A method for providing a modified enkephalin peptide having altered binding affinity..." thereby obviating the need for antecedent basis.

The Examiner notes that claim 55 is directed to reduced binding affinity, and suggests that reduced binding affinity is not consonant with the specification, which appears to be seeking compounds with increased binding affinity. However, the overall thrust of the specification is to provide proteins that traverse the blood brain barrier. In some cases, proteins that more readily traverse the blood brain barrier may have reduced binding affinity and yet be therapeutically superior to the native enkephalin peptide, which does not traverse the blood brain barrier at all. Consequently, the recitation of reduced binding affinity and claim 55 is not inconsistent with the specification.

The Examiner asks for confirmation that all members of the Markush group in claim 57 are proteins or peptides. Claim 57 is canceled, thereby obviating this issue.

10 Fees Payable

Submitted herewith is a check payable to the Commissioner of Patents and Trademarks in the amount of $400.00 which represents the $130.00 Terminal Disclaimer filing fee, the $120.00 1-month extension fee and $150.00 additional claim fees for three additional dependent claims. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 13-4365 of Moore & Van Allen PLLC.

11 Conclusion

The pending claims are now in condition for allowance. In the event that any issues remain incident to formal allowance of the application, the Examiner is requested to contact the undersigned attorney at (919) 286-8104.

Respectfully submitted,

Dated: DECEMBER 15, 2004

By: _____

Jerry W. Clark
Registration No. 52,753
Attorney for Applicants
Moore & Van Allen, PLLC
430 Davis Drive, Suite 500
Morrisville, North Carolina 27560-6832
Phone: (919) 286-8000
Facsimile: (919) 286-8199
Email: jerryclark@mvalaw.com